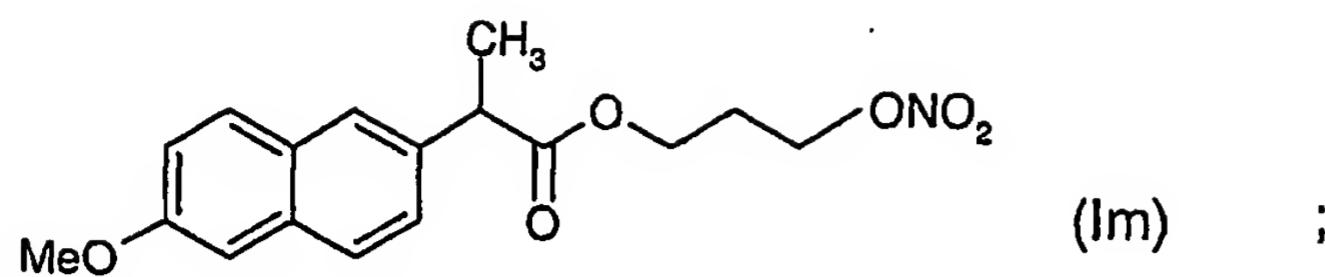
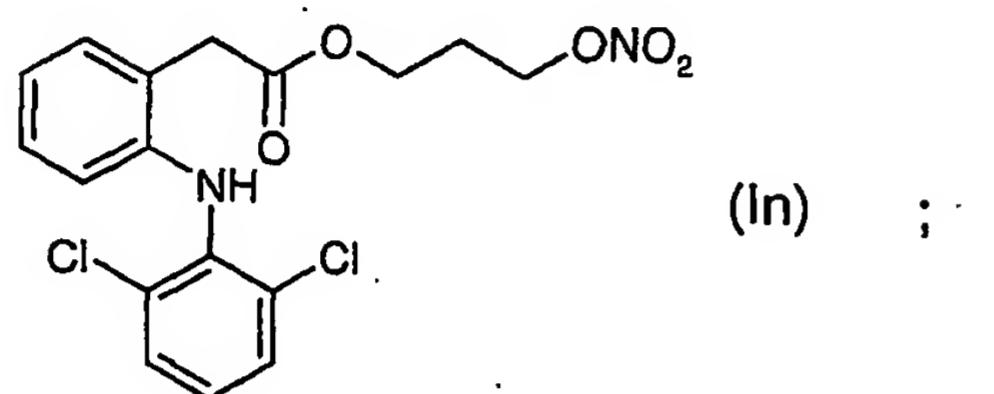


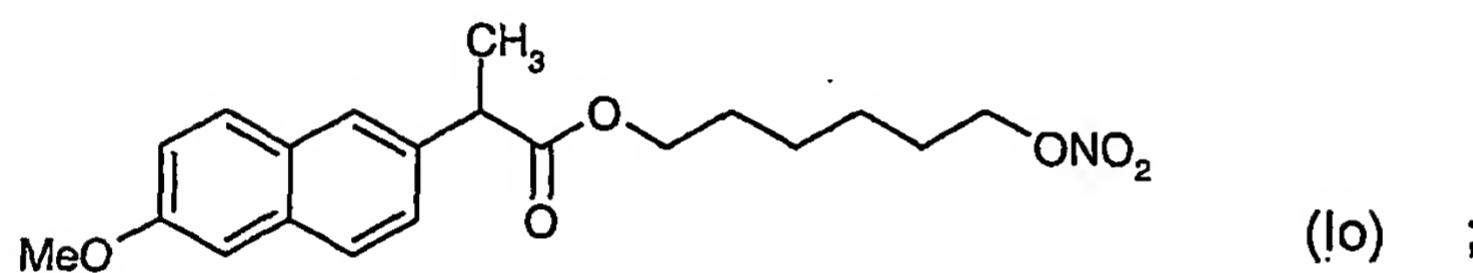
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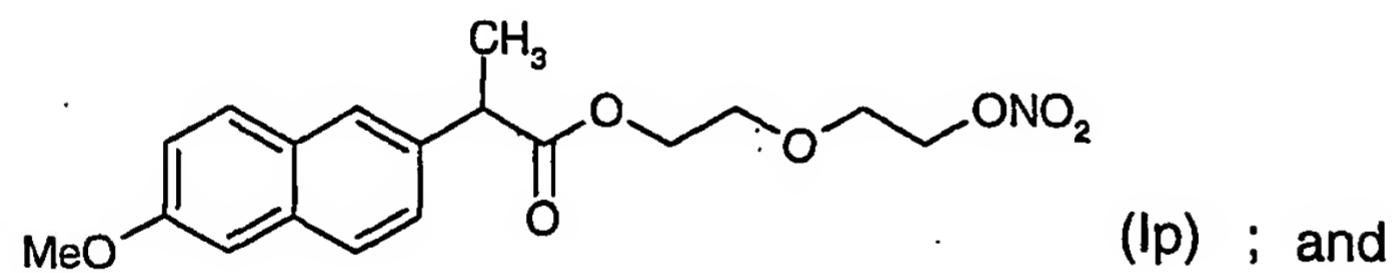
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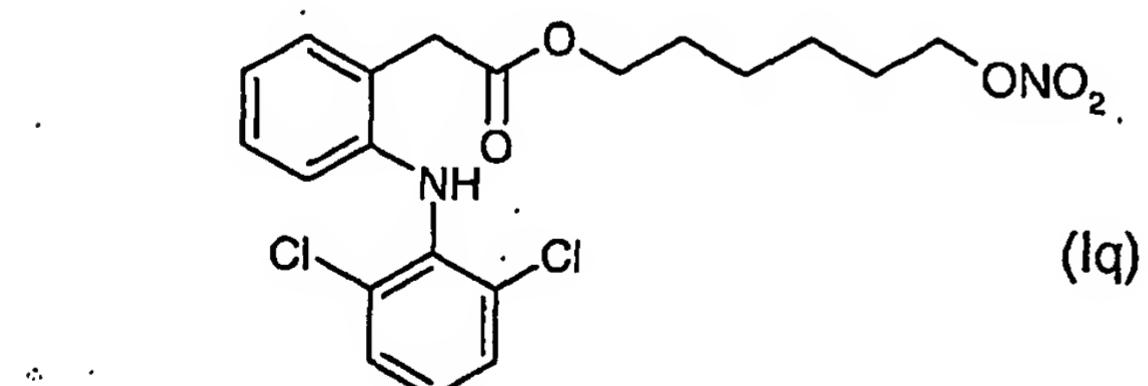
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- NSAIDs are by nature in form of a powder, whereas NO-releasing NSAIDs predominantly provide a compound in semisolid form or in oil form as such, due to the spacer. This unique feature provides the advantage that no external lipophilic oil or semisolid matrix needs to be added to the emulsion pre-concentrate, since this is an inherent feature of the
- 5 drug. Additionally, a pharmacologically inert oil or semisolid fat may be added to the pharmaceutical composition by means of a filler or as a viscosity regulator. A filling agent may be required to increase dosing accuracy for low dose compounds. A viscosity regulator may be required in order to adjust optimal viscosity for filling of the composition into e.g. capsules. In particular high speed liquid filling of capsules requires careful
- 10 adjustment of viscosity within a range that prevents splashing on the low viscosity end and thread-formation on the high viscosity end. Moreover, the viscosity range must be chosen so as to give a pumpable formulation. The viscosity range typically required for liquid filling of capsules is from 0.1 to 25 Pa s.
- 15 The total amount of NO-releasing NSAID(s) used in the composition of the invention is preferably in the range 50-1500 mg per unit dose. In still a further preferred embodiment, the amount of NO-releasing NSAID(s) used in the composition is 125-500 mg per unit dose.
- 20 The wording "unit dose" is defined as the amount of active compound administered in one single capsule, or dissolved in one glass of water.

The wording "phospholipid" is defined as a non-ionic surfactant comprising a phosphatidyl choline, a diglyceride linked to a choline ester of phosphoric acid. Different fatty acids are

25 bound to the glyceride such as stearic acid, palmitic acid, oleic acid, linoleic acid, linolenic acid. The origin of the phospholipid determines the content of the fatty acids linked.

Further, the phosphatidylcholine can be hydrogenated as well, i.e. the fatty acid moieties have been modified. The phospholipids used can be of both natural origin or synthetic.

Natural phospholipids are, for example, lecithin. Natural phospholipids are a mixture of

30 various phospholipids and accompanying substances. The content of phosphatidylcholine

indicates the product, for example, LIPOID E80, denotes composition with egg lecithin comprising a specified mixture of the chains. Any lecithin can be used but the preferred lecithins are from soya or egg. Suitable lecithins are LIPOID® S40 (soya lecithin) and LIPOID® E80 (egg lecithin). The number defines the content of phosphatidylcholine.

5

The wording "surfactant" is defined as surface-active amphiphilic compounds such as block co-polymers. Preferred surfactants in accordance with the present invention are non-ionic surfactants, for example those containing polyethylene glycol (PEG) chains, particularly block co-polymers such as poloxamers.

10

Examples of suitable poloxamers are Poloxamer 407 (Pluronic F127®); Poloxamer 401 (Pluronic L121®); Poloxamer 237 (Pluronic F87®); Poloxamer 338 (Pluronic F138®); Poloxamer 331 (Pluronic L101®); Poloxamer 231 (Pluronic L81®); tetrafunctional polyoxyethylene polyoxypropylene block copolymer of ethylene diamine, known as Poloxamine 908 (Tetronic 908®); Poloxamine 1307 (Tetronic 1307®); Poloxamine 1107 polyoxyethylene polyoxybutylene block copolymer, known as Polyglycol BM45®. This list is only intended to serve as exemplification of surfactants that may be used in accordance with the present invention, and should not in any way be considered as exhaustive or as limiting the invention.

15

Also a co-surfactant may be added the surfactant above. The co-surfactant has a property as an enhancer of the emulsifying effect of the surfactant. Co-surfactant suitable for the unit dosage form of the invention is, for example, caprylocaproyl macroglycerides.

20

25 The total amount of surfactant(s) per unit dosage form in accordance with the invention may be within the range of from 12.5-6000 mg, preferably of from 100-500 mg. The amount phospholipid is 5-20% by weight, of the total amount of surfactants. The ratio NO-releasing NSAID:phospholipid/surfactant may vary from 1:0.1 to 1:10, preferably from 1:0.3 to 1:3.

30

All phospholipids, surfactants and co-surfactants described above are commercially available from e.g. LIPOID, BASF, Dow Chemicals, and Gattefossé.

In one aspect of the present invention, an oily (lipophilic) or semi-solid NO-releasing

- 5 NSAID is used as the active ingredient.

If additional oil is added to the pharmaceutical composition this may be any oil as long as it is inert and compatible with the capsule material, as well as being acceptable for use in pharmaceuticals. A person skilled in the art will appreciate which oil to select for the

- 10 intended purpose. Examples of suitable oils that may be used in accordance with the present invention are vegetable oils such as coconut oil, corn oil, soybean oil, rape seed oil, safflower oil and castor oil. Also animalic oils such as fish oil or one or more mono-, di- and triglycerides are suitable for the purposes of the present invention.

- 15 If a semi-solid fat is used as a filler for the pharmaceutical composition, this may preferably be selected from mono-, di- and triglycerides, and fatty acid alcohol such as stearyl alcohol, Gelucires 33/01<sup>®</sup>, 39/01<sup>®</sup>, 43/01<sup>®</sup>, glyceryl palmitostearate such as Precirol ATO5<sup>®</sup>. Gelucire<sup>®</sup> is a mixture obtained by mixing mono-, di-, and tri-esters of glycerol, mono- and di-esters of polyethylene glycol, or free polyethylene glycol.

20

If an additional oil or semi-solid fat is used in the pharmaceutical composition according to the invention, this may serve as a filler or as a viscosity regulator.

- The wording "short-chain alcohols" used in accordance with the present invention is herein defined as linear or branched mono-, di- or tri-alcohols having 1-6 carbon atoms. Examples of such short-chain alcohols useful in accordance with the invention are ethanol, propylene glycol and glycerol.

- 30 If a short-chain alcohol is added to the pharmaceutical composition according to the invention, the solubility is enhanced and a smaller amount of surfactant is required.

- In another aspect of the invention, two or more NO-releasing NSAIDs are used as active ingredients, where anyone of said drugs may be present as an oil or as a semi-solid, or where at least one of said drugs is present as an oil or as a semi-solid and the other one(s) 5 may be present as a solid which is dissolved or suspended in the oily or semi-solid compound. Combinations of two or more NO-releasing NSAIDs may be advantageous in case the high NO-load of a high-dose low potent NO-releasing NSAID is desired to be supplemented with a low dose of high potent NO-releasing NSAID.
- 10 A further aspect of the invention is a combination of one or more NO-releasing NSAIDs and an acid susceptible proton pump inhibitor (PPI) compound. The NO-releasing NSAIDs should be formulated such that it is emulsified in the stomach, i.e. as a SEDDS formulation as described above, while the acid susceptible proton pump inhibitor (PPI) must be protected from contact with the acidic gastric juice by for instance an enteric coating. The 15 enteric coating layered PPI remain unaffected until it reaches the intestine, where the PPI is released. Individually prepared enteric coating layered units of the proton pump inhibitor (PPI) may be mixed into the SEDDS melt. Alternatively the PPI's may be filled into a capsule filled with solidified SEDDS, where a layer of protective paraffin may be needed between SEDDS and the prepared PPI pellets. In still an alternative embodiment the 20 prepared PPI pellets may be mixed into a liquid SEDDS formulation.

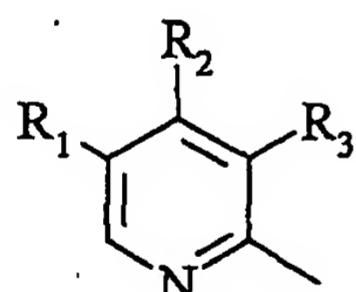
The combination may thus either be a fix combination, i.e. as a formulation where the NO-releasing NSAID(s) and the acid susceptible proton pump inhibitor are mixed and thereafter filled into a suitable dosage unit. In an alternative embodiment of the invention 25 the acid susceptible proton pump inhibitor may be filled into a capsule with an already solidified SEDDS formulation of one or more NO-releasing NSAID(s) – in this case a layer of protective paraffin or other inert material may be required between the SEDDS formulation and the acid susceptible proton pump inhibitor. In still an alternative embodiment the acid susceptible proton pump inhibitor is mixed into a liquid SEDDS 30 formulation of the NO-releasing NSAID(s).

- In an alternative embodiment of the invention, the NO-releasing NSAID(s) and the PPI may be provided in form of a kit, where the NO-releasing NSAID and the PPI are administered sequentially, i.e. one after the other. The order of administration is not crucial, meaning that either of the NO-releasing NSAID or the PPI may be administered before the other. Thus, one embodiment of the invention comprises a combination treatment where one or more NO-releasing NSAIDs are administered to a patient in need of treatment, whereafter a PPI is administered, or vice versa.
- 5 Examples of proton pump inhibitors suitable in a combination with a NO-releasing NSAID in accordance with the present invention as stated above, is a compound of the general formula II or a pharmaceutically acceptable alkaline salt thereof, or one of its single enantiomer or an alkaline salt of the single enantiomer:
- 10

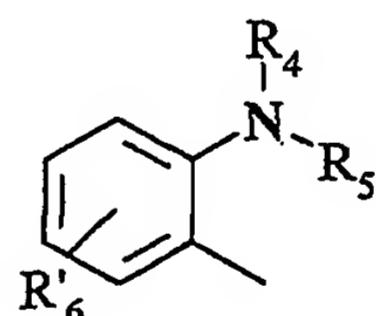


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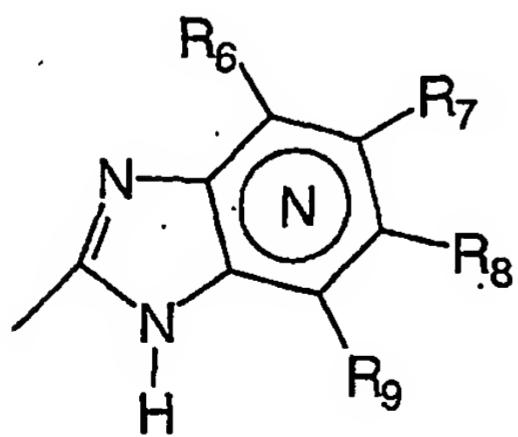
$\text{Het}_1$  is



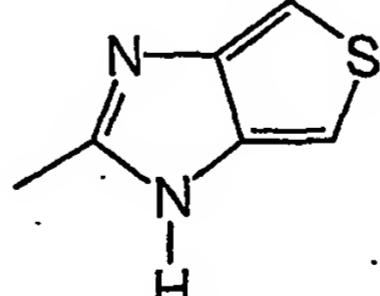
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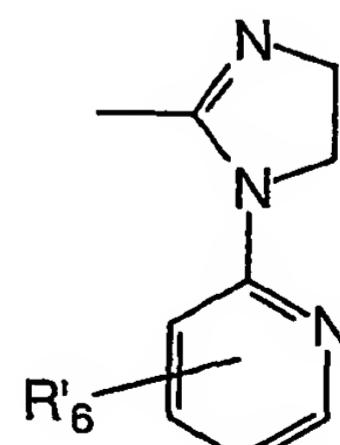
20  $\text{Het}_2$  is



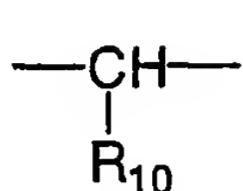
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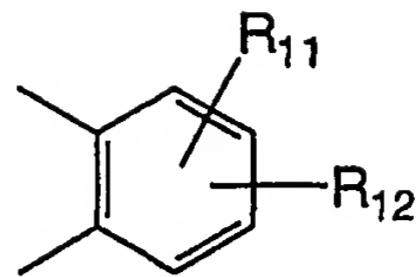
or



$\text{X} =$



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R<sub>6</sub>-R<sub>9</sub>

- 5     optionally may be exchanged for a nitrogen atom without any substituents;

R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are the same or different and selected from hydrogen, alkyl, alkoxy  
optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino,  
morpholino, halogen, phenyl and phenylalkoxy;

10

R<sub>4</sub> and R<sub>5</sub> are the same or different and selected from hydrogen, alkyl and aralkyl;

R<sub>6</sub>' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

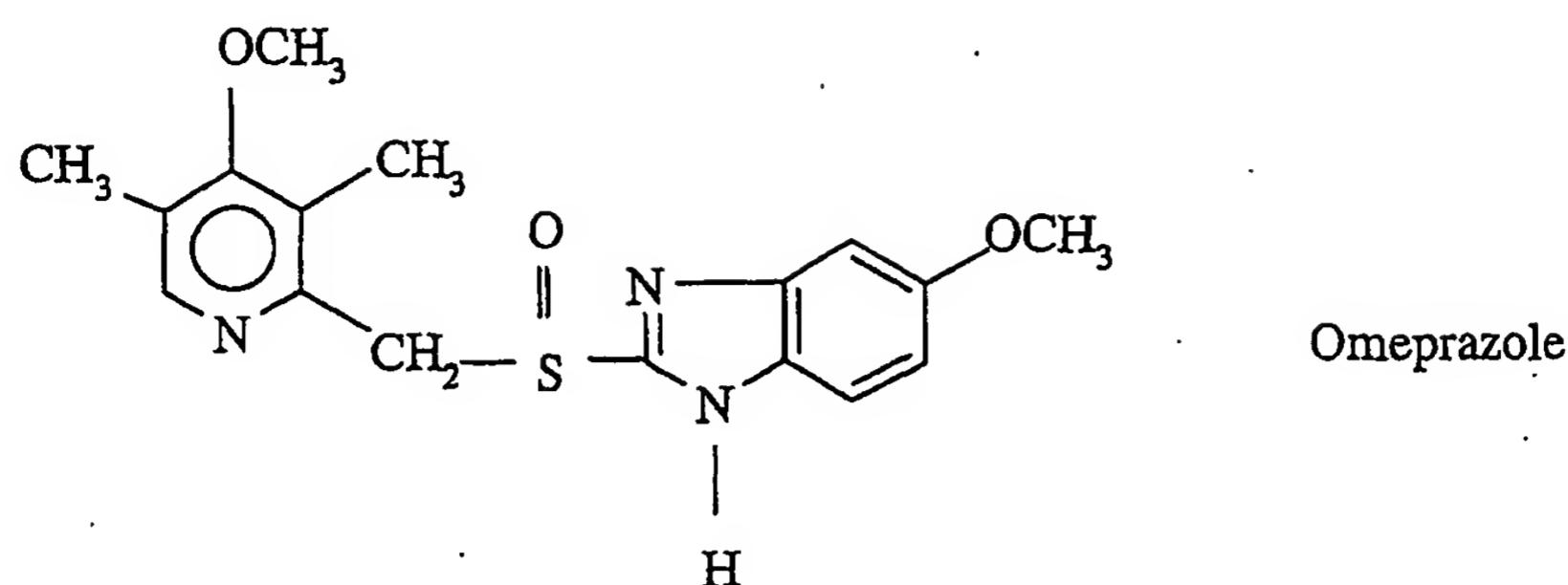
- 15    R<sub>6</sub>-R<sub>9</sub> are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-  
alkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R<sub>6</sub>-R<sub>9</sub>  
form ring structures which may be further substituted;

R<sub>10</sub> is hydrogen or forms an alkylene chain together with R<sub>3</sub> and

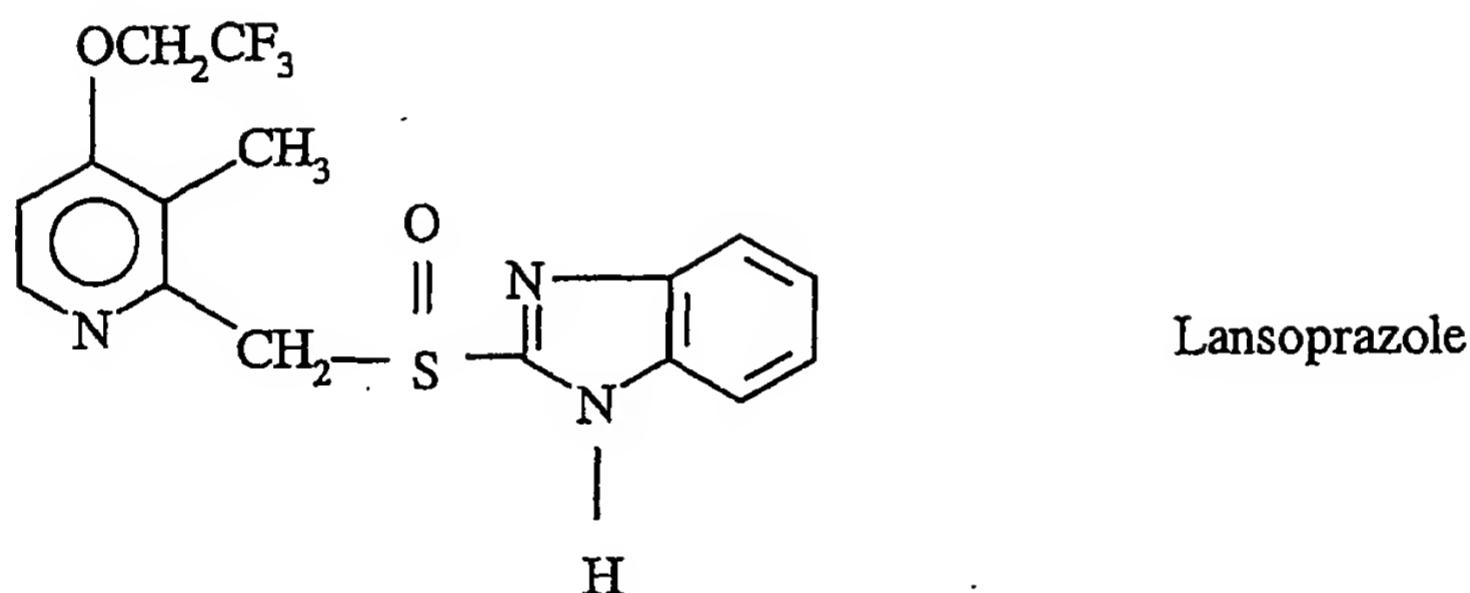
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R<sub>11</sub> and R<sub>12</sub> are the same or different and selected from hydrogen, halogen or alkyl;  
alkyl groups, alkoxy groups and moieties thereof, they may be branched or straight C<sub>1</sub> - C<sub>9</sub>  
-chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

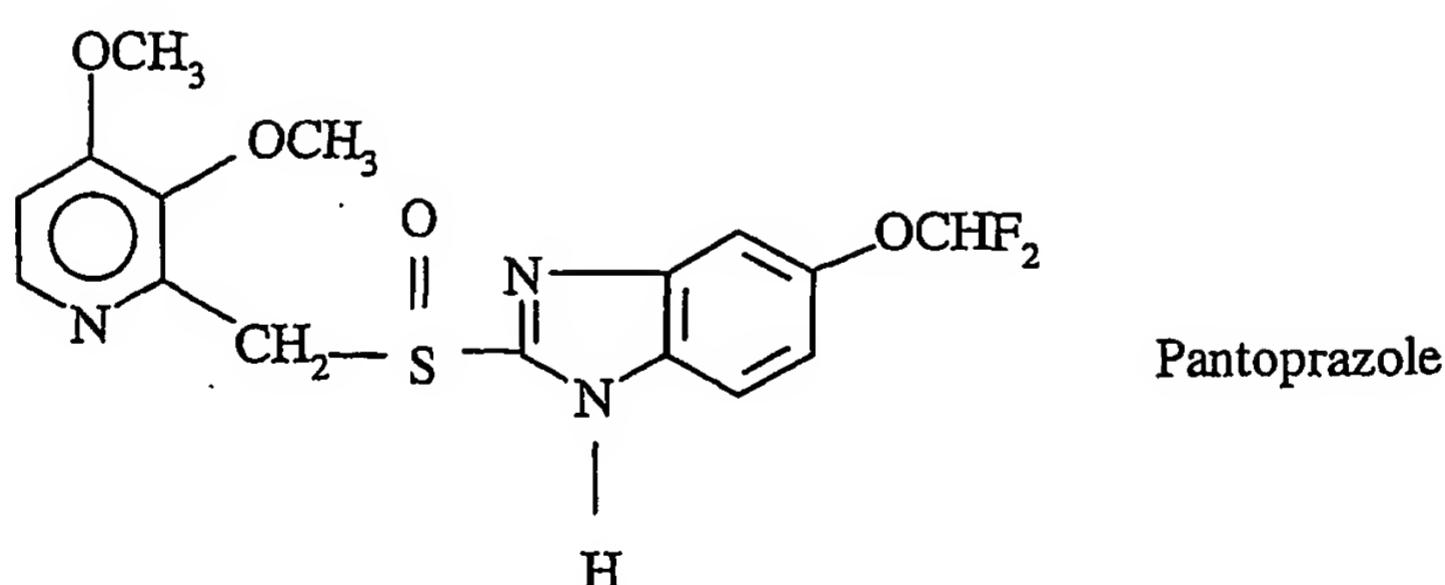
- 25    Examples of specific proton pump inhibitors suitable in accordance with the present  
invention are

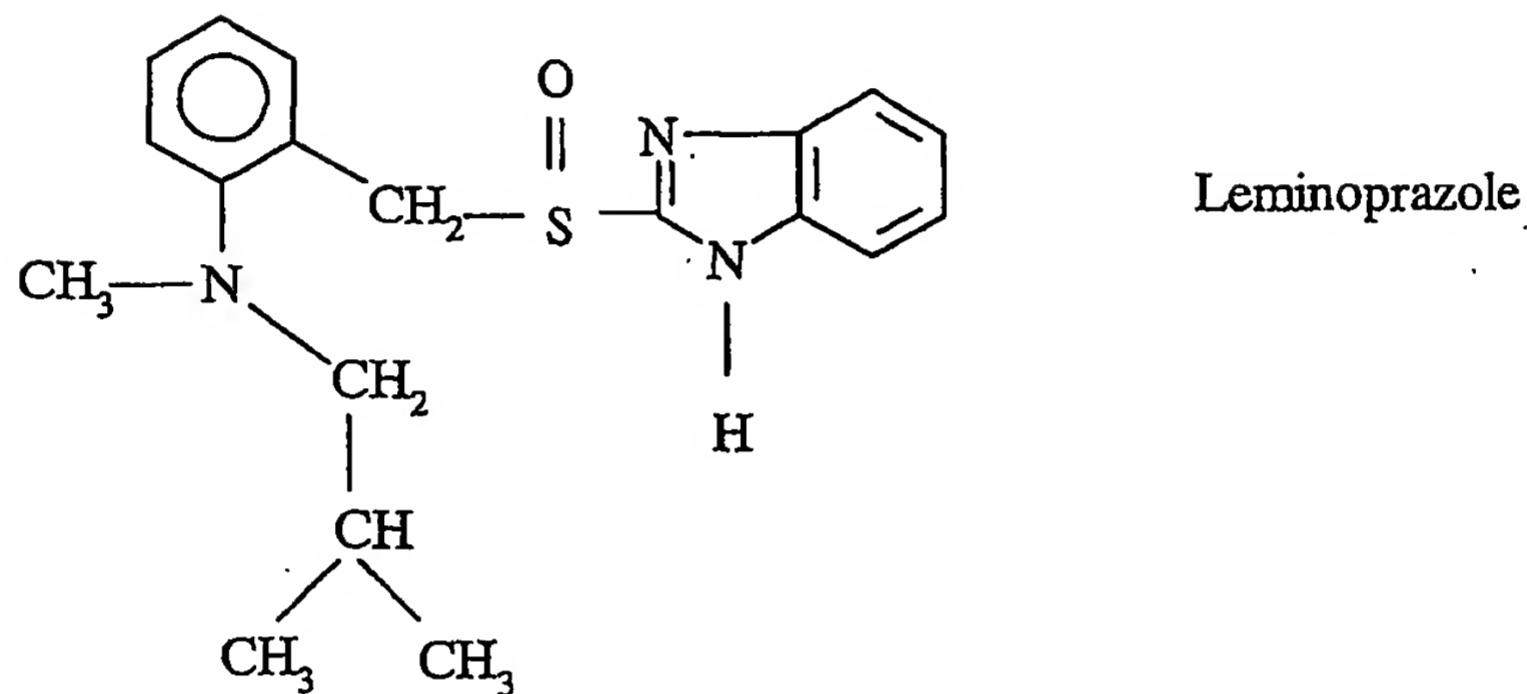
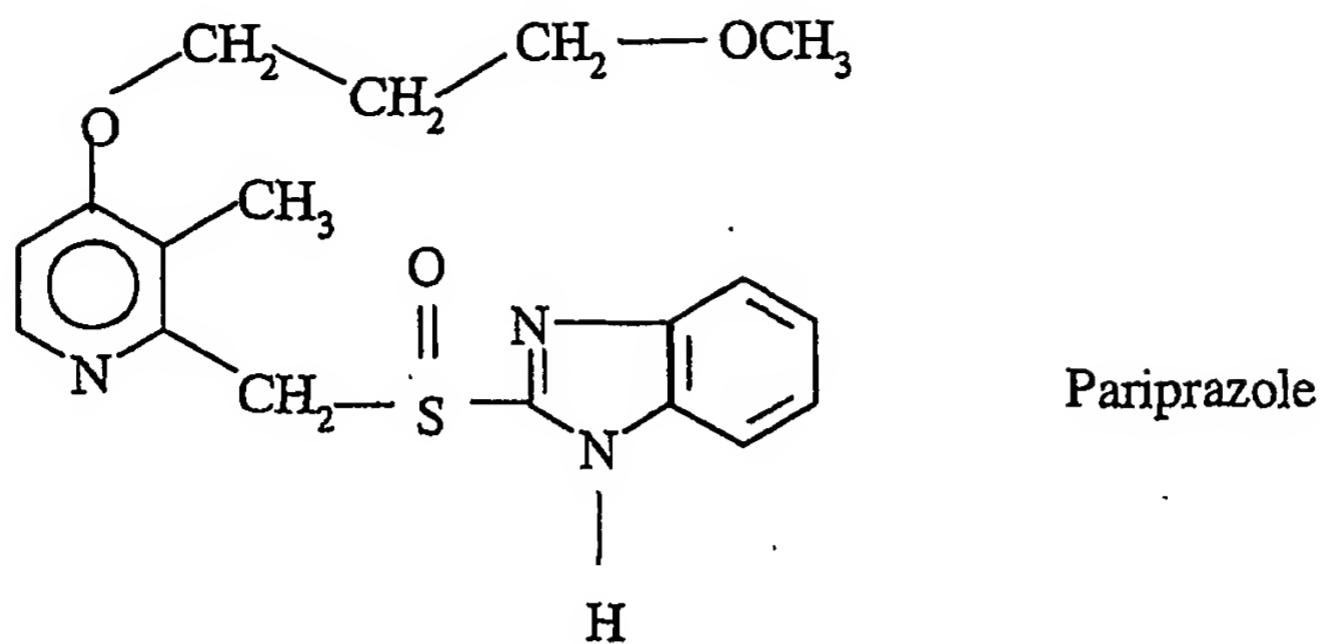


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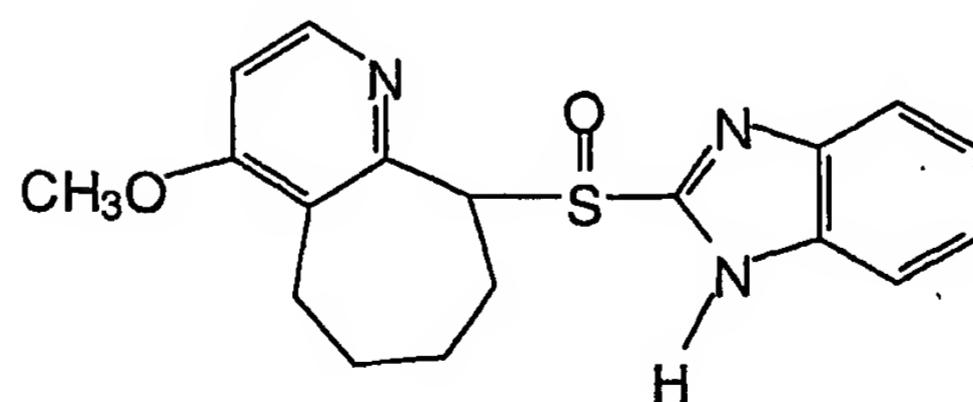
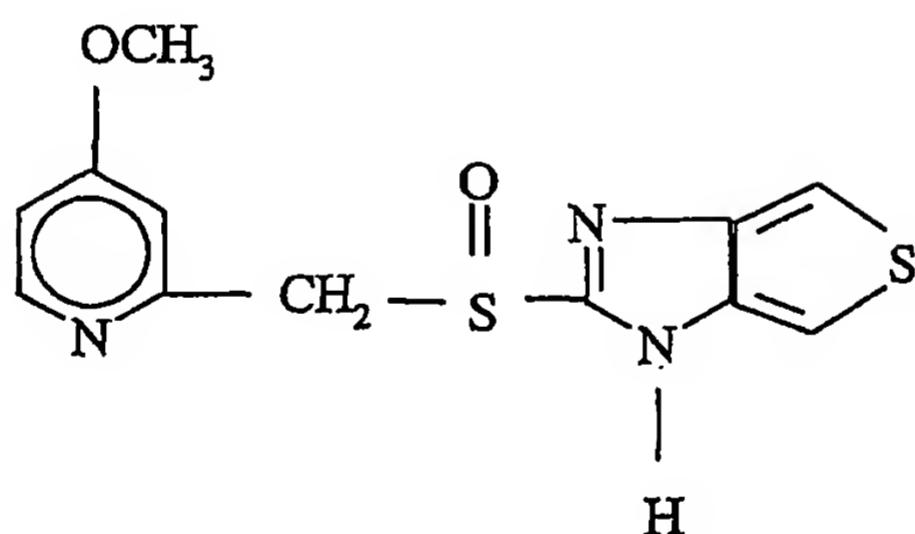


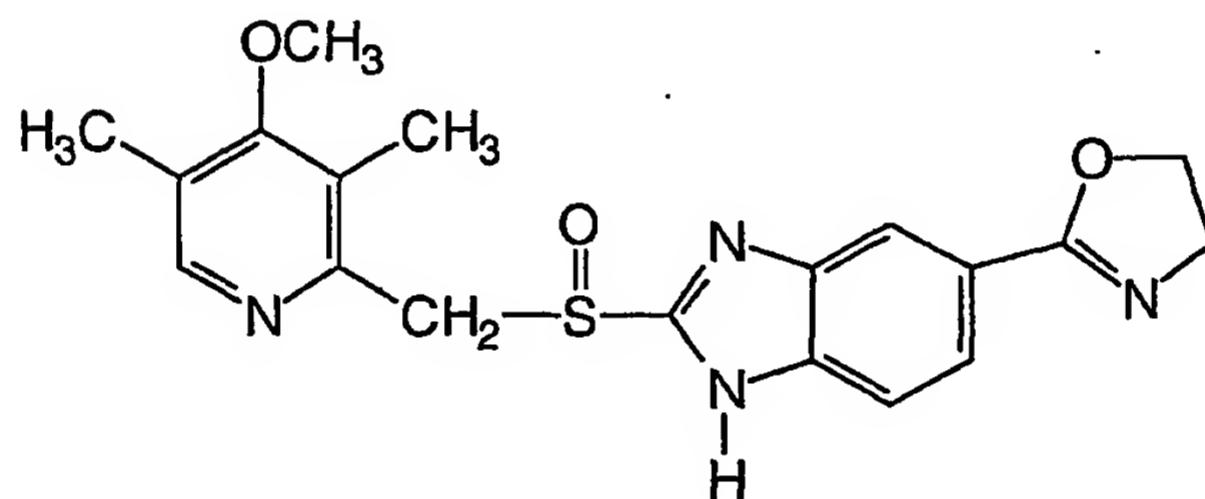
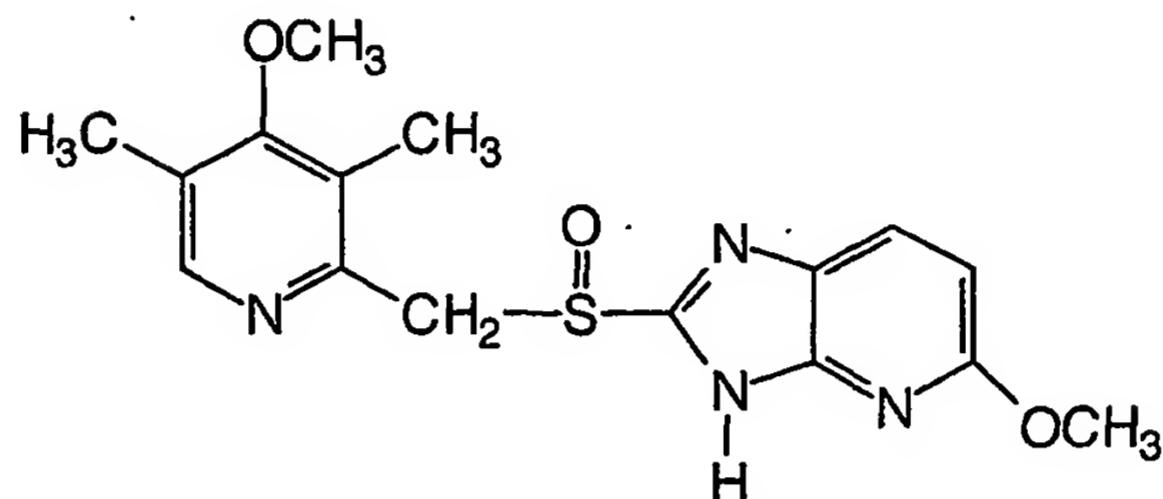
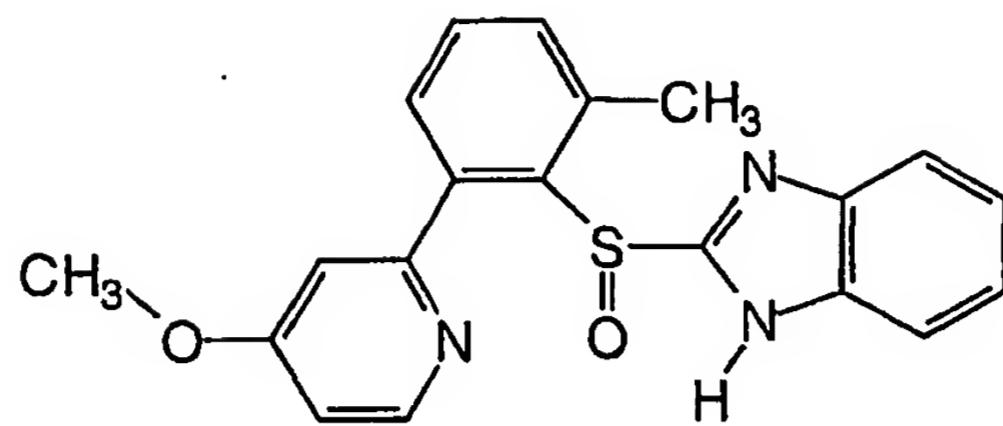
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The acid susceptible proton pump inhibitors used in the dosage forms of the invention may be used in their neutral form or in the form of an alkaline salt, such as for instance the  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Na}^+$ ,  $\text{K}^+$  or  $\text{Li}^+$  salts, preferably the  $\text{Mg}^{2+}$  salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of the 10 substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO 90/06925, and further especially suitable compounds are described in WO 95/01977 and WO94/27988.

15

The proton pump inhibitors used in a combination in accordance with the present invention, are preferably provided as enteric coating layered pellets comprising the acid

susceptible proton pump inhibitor. For the composition of the enteric coating layered pellets and its preparation, reference is made to WO 96/01623, which is hereby incorporated by reference.

- 5 Suitable combinations in accordance with the present invention are for instance a NO-releasing NSAID of the formula Ia and omeprazole or an alkaline salt of omeprazole, (S)-omeprazole or an alkaline salt of (S)-omeprazole; or a NO-releasing NSAID of the formula Ii and omeprazole or an alkaline salt of omeprazole, (S)-omeprazole or an alkaline salt of (S)-omeprazole.

10

The pharmaceutical composition of the invention is filled into unit dosage forms suitable for oral administration, such as capsules, drinking ampoules and dose cushions, or may be formulated as other suitable oral unit dosage forms such as chewable soft pills and chewy-base lozenges.

15

In a preferred embodiment of the invention, the pharmaceutical composition is filled into hard gelatine capsules, but capsules from alternative materials such as methyl cellulose-based shells, and soft gelatine capsules may also be used.

- 20 In an alternative embodiment of the invention, the pharmaceutical composition may be dissolved in e.g. a glass of water, thus allowing the pre-concentrate to form an emulsion which may be administered as such. The compositions intended for dissolution prior to administration may be filled e.g. into soft gelatine capsules, plastic or aluminium cushions, or plastic or glass ampoules. This feature is particularly advantageous for high dose compositions, which would require a large capsule, for patients who have difficulty in swallowing capsules, and for paediatric patients.
- 25

In a preferred embodiment the pharmaceutical composition of the present invention is filled into capsules. Preferred capsules are gelatine capsules, which may be soft or hard.

- 30 The hard gelatine capsule consists of two pieces, a cap and a body, one fitting inside the

other. The hard gelatine capsules are produced empty and filled in a separate operation step. The soft gelatine capsule is a capsule, which is manufactured and filled, in one single operation.

- 5 As mentioned above, the emulsion pre-concentrate transforms into an oil-in-water emulsion upon contact with the gastrointestinal fluids, whereby the active drug is released. Thus, the composition will form an *in situ* oil-in-water emulsion in the gastrointestinal tract (GI tract).
- 10 The pharmaceutical composition of the present invention is particularly useful in the treatment of pain and inflammation. The wording "pain" is intended to include, but not limited to, nociceptive and neuropathic pain or combinations thereof; acute, intermittent and chronic pain; cancer pain; migraine and headaches of similar origin. The wording "inflammation" is intended to include, but not limited to, rheumatoid arthritis;
- 15 osteoarthritis; and juvenile arthritis:

#### Methods of preparation

The pharmaceutical composition of the present invention may be prepared mainly by the following alternative methods:

20

##### *I. Mixing*

- a) The oily or semi-solid NO-releasing NSAID is put in a vessel, phospholipid, and optionally, a solid, semi-solid surfactant or solid/oily fat is added. The mixture is gently heated, making the formulation fluid, mixed thoroughly until homogenous (visual inspection) and the pre-concentrate is filled into capsules suitable for oral administration.
- 25 b) Alternatively, the oily NO-releasing NSAID is put in a vessel and phospholipid, and optionally, a fluid surfactant is added. The mixture is mixed thoroughly until homogenous (visual inspection) and the pre-concentrate is filled into capsules suitable for oral administration.

30

c) In a further alternative method, the oily NO-releasing NSAID is put in a vessel together with phospholipid, and finely grinded (particle size < 177 um) solid surfactant is added. The liquid mixture is mixed thoroughly until homogenous (visual inspection) and the pre-concentrate is filled into capsules suitable for oral administration.

5

d) In still an alternative method the phospholipid and optionally, a semi-solid/solid surfactant (s) are put in a vessel, and one or more alcohols are added. The mixture is heated to the temperature corresponding to the melting point of the excipients, making the formulation fluid, mixed thoroughly until homogenous (visual inspection). The NO-releasing NSAID is added, and the mixture is mixed thoroughly until homogenous (visual inspection). The pre-concentrate is filled into capsules suitable for oral administration.

e) In yet a further alternative method the phospholipid optionally in mixture with a liquid surfactant(s) is put in a vessel, and one or more alcohols are added. The mixture is blended thoroughly until homogenous (visual inspection). The NO-releasing NSAID is added, and the mixture is mixed thoroughly until homogenous (visual inspection). The pre-concentrate is filled into capsules suitable for oral administration.

In order to fill a two-piece capsule or a soft gel capsule with a liquid, the formulation must be within a certain viscosity range, as determined by the manufacturer, at the filling 20 temperature suitable for the process. For a two-piece capsule the maximum filling temperature is roughly 70 °C. The viscosity of the formulation should normally be in the range 50-1000 cPoise (=0.05-1 Pas) at the temperature chosen for the filling process.

For the filling of the formulation into soft gel capsules, process temperature is not allowed 25 to exceed 30-40 °C (the exact temperature depending on the manufacturer). The formulation must be liquid and have a viscosity that allows it to be pumpable at the filling temperature. In order to make the formulation liquid with an acceptable viscosity, several additives may be used, for example Cremophor EL<sup>®</sup> or fractionated coconut oil.

## *II. Filling*

For the filling procedure it is required that the composition is in liquid form at the temperature of filling. Semisolid thermosoftening compositions are therefore filled above the liquefying temperature. Soft gelatine capsules are manufactured and filled in one operation, and may be filled at temperatures of up to 40 °C, whereas hard gelatine capsules may be filled at temperatures of up to 70 °C. Hard gelatine capsules filled with compositions that remain liquid at storage temperature require sealing, e.g. by gelatine banding, to prevent leakage. The process of liquid filling of hard gelatine capsules and product requirements are e.g. described in *W.J. Bowtle, Pharmaceutical Technology Europe, October 1998; V.M. Young, Pharmaceutical Manufacturing and Packaging Sourcer, March 1999; and E.T. Coole, Pharmaceutical Technology International, September/October 1989*. Using two piece capsules permits filling of more than one phase into a single capsule, which may be desired for bi- or multiphase drug release (*W.J. Bowtle et al., Int. J. Pharm. 141 (1996), pp. 9-16*). Several phases of solidifying material can be filled in single steps. The final phase may be liquid if required. The number of phases is only restricted by the capsule size, and volume of the single phases. This special feature may also allow controlled release or separation of different drug substances formulated in the same capsule. Additionally, capsules may be processed further, e.g. by enteric coating.

## *III. Combination with PPI's*

The oily or semi-solid NO-releasing NSAID is put in a vessel, phospholipid and optionally a solid or semi-solid surfactant and optionally a solid/oily fat is added. The mixture is gently heated, making the formulation fluid, mixed thoroughly until homogenous (visual inspection) and prepared enteric coating layered pellets comprising an acid susceptible proton pump inhibitor are added to the mixture. The pre-concentrate with the suspended PPI-pellets is filled into capsules, where it solidifies, suitable for oral administration.

Alternatively the oily or semi-solid NO-releasing NSAID is put in a vessel, solid surfactant and solid/oily fat (optional) is added. The mixture is heated to the temperature corresponding to the melting point of the excipients, making the formulation fluid, mixed

thoroughly until homogenous (visual inspection). The pre-concentrate is filled into capsules suitable for oral administration, where it solidifies. A protective layer of paraffin, or any other inert thermo softening base suitable for oral administration, is added and allowed to solidify. On top of the paraffin, the prepared PPI-pellets are added.

5

In still an alternative method, the oily NO-releasing NSAID is put in a vessel, phospholipid and optionally a fluid surfactant are added. The mixture is mixed thoroughly until homogenous (visual inspection), and the prepared PPI-pellets are added to the mixture. The pre-concentrate with suspended PPI-pellets is filled into capsules suitable for oral 10 administration.

#### *IV. Characterisation of the formulations*

In order to characterise formulations, the time required for the formulation to form an oil-in-water emulsion upon contact with simulated gastric fluid, SGF, (without enzymes), is determined, and the formed emulsion is characterised. SGF comprises of 7 millilitres concentrated hydrochloric acid, 2 grams of sodium chloride and distilled water to give the solution a total volume of 1 L. The "emulsion-forming test" is performed in test tubes (beaker) with magnetic stirring. The test tube, containing a small magnet, is filled with 12.5 ml SGF without enzymes, corresponding to one tenth of the average volume of gastric fluid in humans, and formulation corresponding to one tenth of the dose of active compound is added. If the formulation being characterised is a combination with a PPI, the PPI-pellets are checked in order that they are unaffected by the SGF, which is made by visual inspection. If the enteric coating of the PPI-pellets is affected, the PPI may be affected negatively in pH=1.2, and this can be observed as a marked change in colour.

25

The time for emulsion formation will vary from 30 seconds and up to 15 minutes, depending on the composition of the formulation. If one or more short-chain alcohols are added, the time for emulsion formation will vary between 2-3 seconds and 3-4 minutes.

30

Detailed description of the invention

The invention will now be described in more detail by the following examples, which are not to be construed as limiting the invention.

5

In the following examples, the active compound used in the formulation was a compound of the formula (Ia) above.

Formulations were prepared by dissolving the phospholipid in a co-solvent such as

10 propylene glycol, glycerol or ethanol, and then adding the active compound to the mixture:

***Formulation 1***

Lipoid S100	0.30 g
Propylene glycol	0.90 g
15 Compound of formula Ia	4.00 g

***Formulation 2***

Lipoid S100	0.30 g
20 Glycerol	0.90 g
Compound of formula Ia	4.00 g

***Formulation 3***

Lipoid S100	0.24 g
25 Etanol	0.96 g
Compound of formula Ia	4.00 g

*Formulation 4*

Lipoid E80	0.30 g
Propylene glycol	0.90 g
Compound of formula Ia	4.00 g

5

*Formulation 5*

Lipoid E80	0.30 g
Glycerol	0.90 g
Compound of formula Ia	4.00 g

10

*Formulation 6*

Lipoid E80	0.30 g
Ethanol	0.90 g
Compound of formula Ia	4.00 g

15

*Formulation 7*

Lipoid S75	0.30 g
Propylene glycol	0.90 g
Compound of formula Ia	4.00 g

20

*Formulation 8*

Lipoid S75	0.30 g
Glycerol	0.90 g
Compound of formula Ia	4.00 g

25

*Formulation 9*

Lipoid S75	0.30 g
Ethanol	0.90 g
Compound of formula Ia	4.00 g

30

The emulsifying formulations were tested in a self-emulsifying test (described on page 24)

The dissolution of the drug was measured according to the paddle method in US Pharmacopoeia (US Pharmacopoeia 24/NF 19, 200).

5

<b>Formulation</b>	<b>Time to emulsion formation</b>	<b>Amount (%) dissolved drug after 200 minutes</b>
1	1-2 minutes	6-8
2	1-2 minutes	6-7
3	1-2 minutes	8-10
4	1-2 minutes	8-10
5	1-2 minutes	8-10
6	1-2 minutes	8-10
7	1-2 minutes	10-13
8	1-2 minutes	8-10
9	1-2 minutes	10-13

The bioavailability of the formulations according to the present invention may be tested by oral administration in fastened minipigs.

Claims

1. A pharmaceutical composition suitable for oral administration, in form of an emulsion  
5 pre-concentrate, comprising
  - (i) one or more NO-releasing NSAID(s);
  - (ii) a phospholipid;

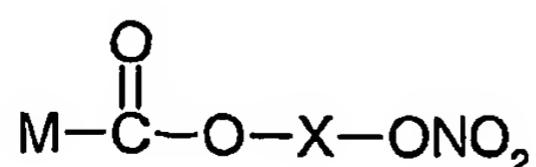
10 said composition forming an *in-situ* oil-in-water emulsion upon contact with aqueous media such as gastrointestinal fluids.

2. A pharmaceutical composition according to claim 1, comprising  
15 (i) one or more NO-releasing NSAID(s);  
(ii) a phospholipid  
(iii) one or more surfactants.

3. A pharmaceutical composition according to any one of claims 1-2, further comprising  
20 an oil or a semi-solid fat.

4. A pharmaceutical composition according to any one of claims 1-3, further comprising one or more short-chain alcohols.  
25

5. A pharmaceutical composition according to any one of claims 1-4, wherein the NO-releasing NSAID is a compound of the formula I



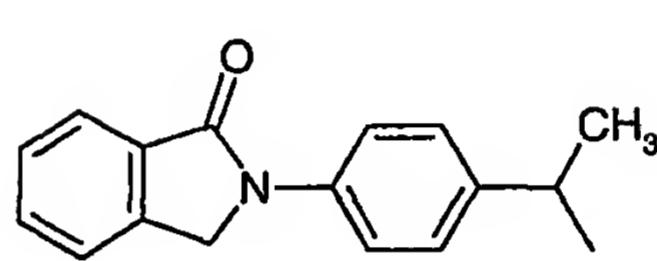
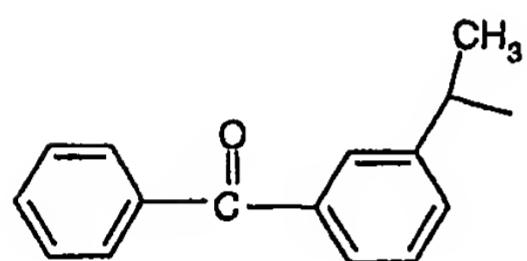
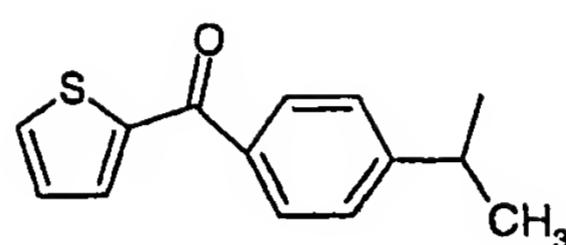
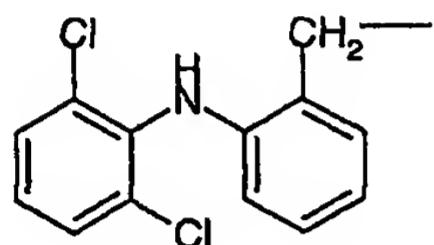
I

wherein

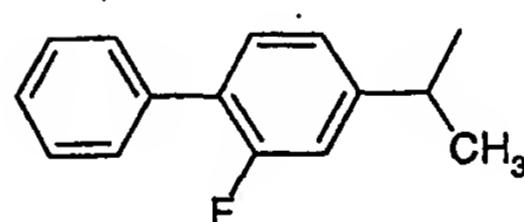
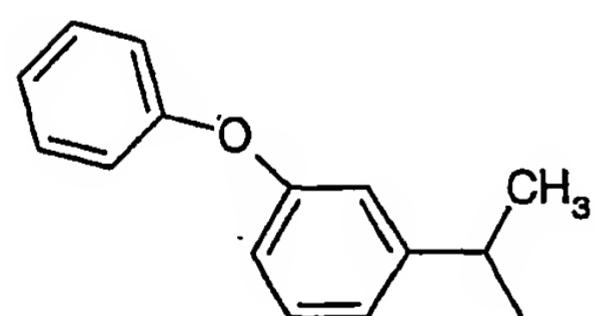
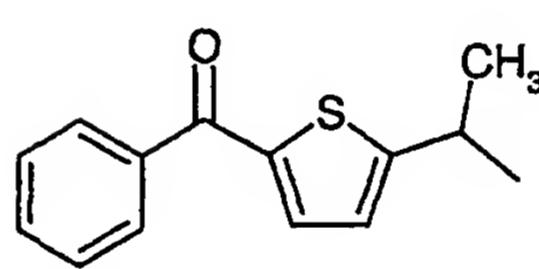
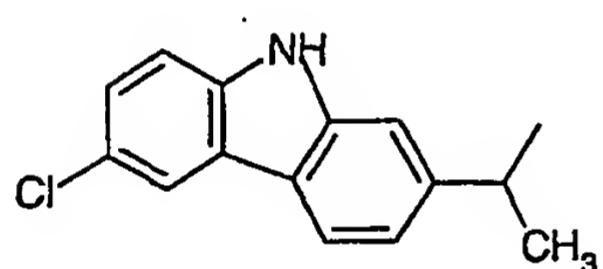
X is a spacer; and

M is selected from anyone of

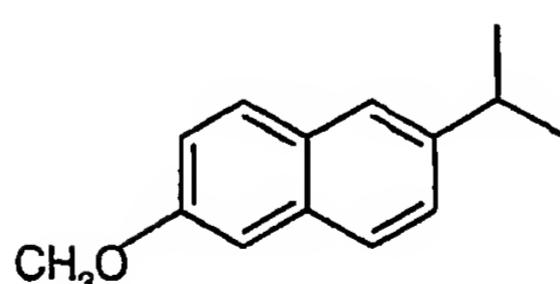
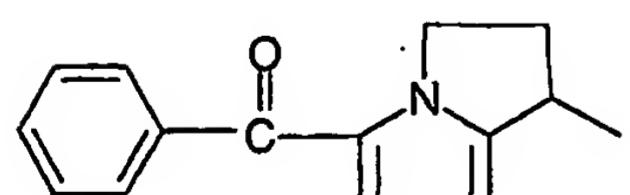
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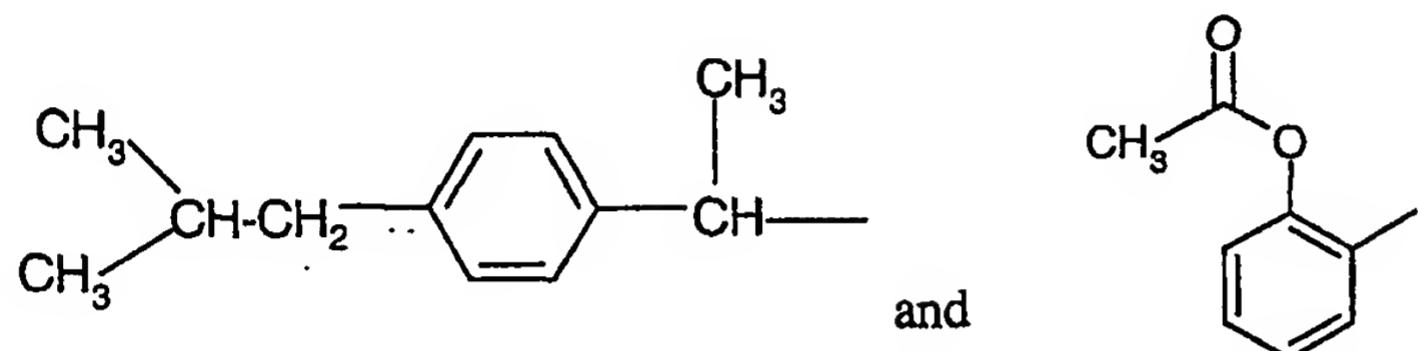
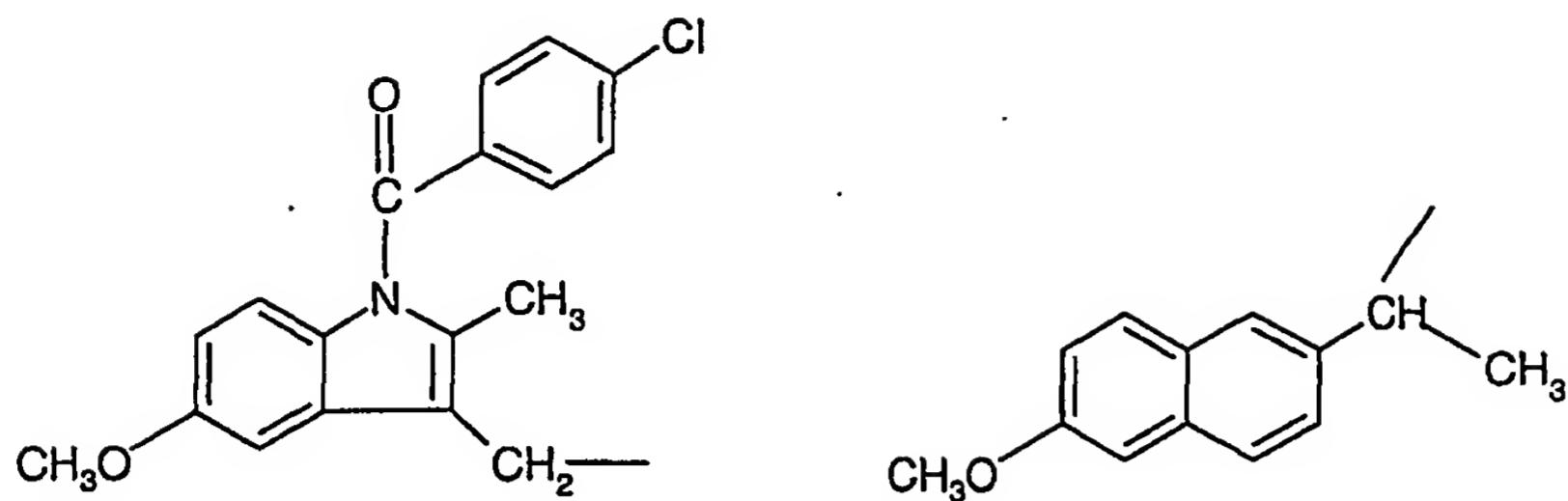


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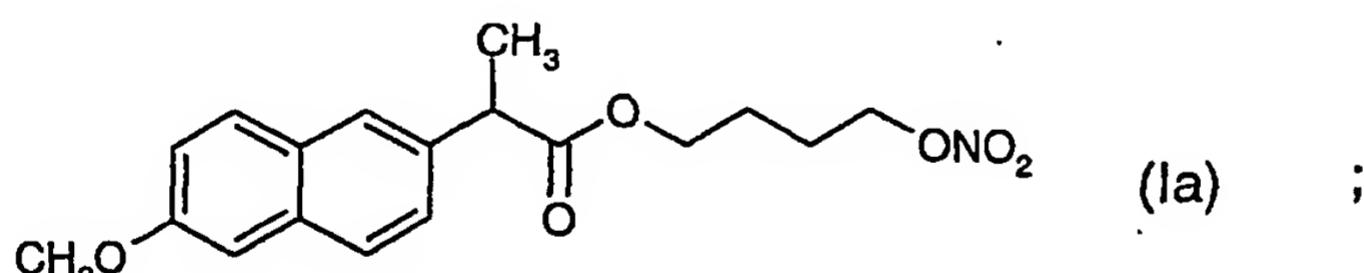
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6. A pharmaceutical composition according to claim 5, wherein the spacer X of the NO-releasing NSAID is selected from a linear, branched or cyclic alkylene group:  $(CH_2)_n$  wherein n is an integer of from 2 to 10;  $-(CH_2)_m-O-(CH_2)_p-$  wherein m and p are integers of from 2 to 10; and  $-(CH_2)_p-C_6H_4-CH_2-$  wherein p is an integer of from 2 to 10.

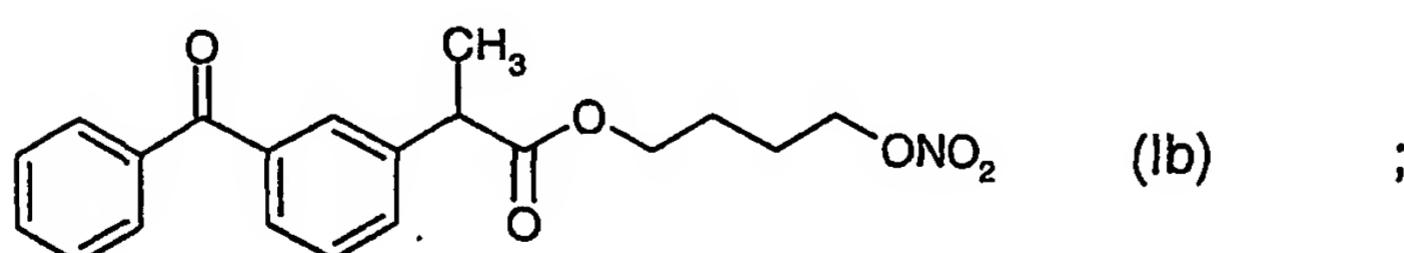
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7. A pharmaceutical composition according to any one of claims 1-6, wherein the NO-releasing NSAID is any one compound selected from

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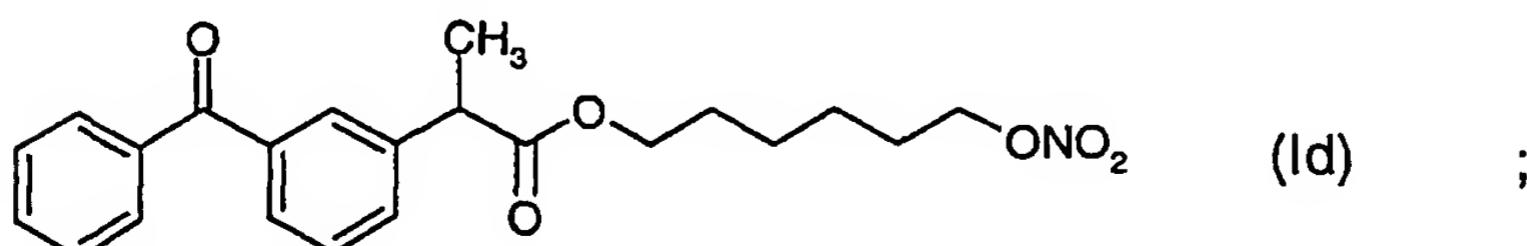


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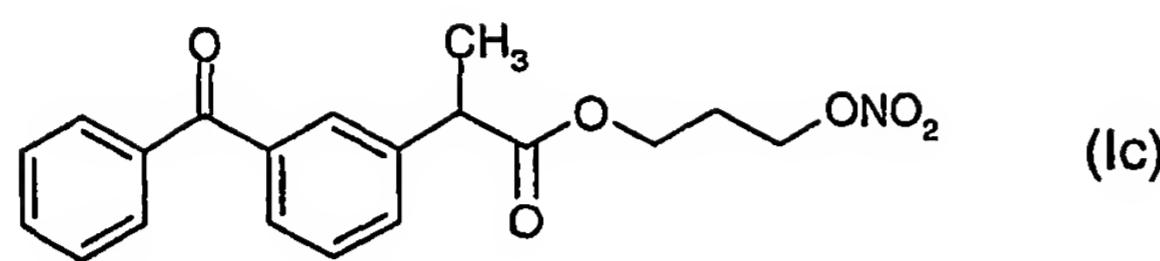
(Ib);

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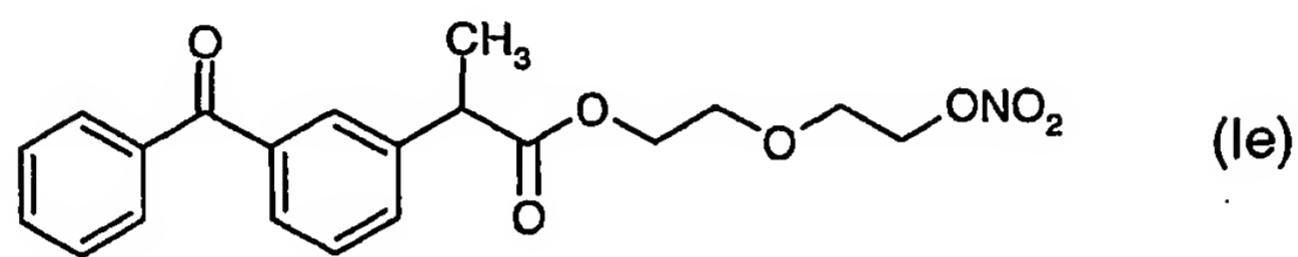
(Id);

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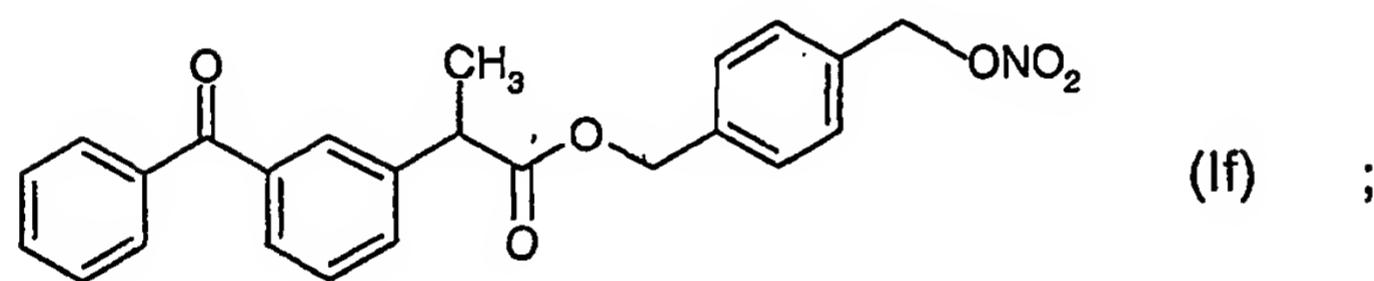
(Ic)

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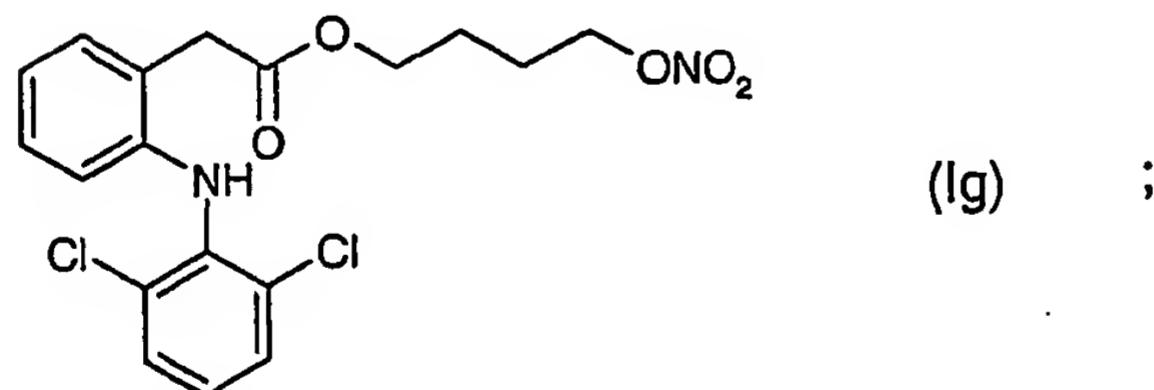
(Ie)

;



(If)

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(Ig)

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